Glass and Ceramics, Vol. 69, Nos. 1 – 2, May, 2012 (Russian Original, Nos. 1 – 2, January – February, 2012)

BIOMATERIALS

UDC 666.1.037.97:666.1.189.43

GLASSY MICROSPHERES WITH ELEVATED YTTRIUM OXIDE CONTENT FOR NUCLEAR MEDICINE

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Translated from *Steklo i Keramika*, No. 2, pp. 3 – 7, February, 2012.

Yttrium aluminosilicate (YAS) glasses with yttrium oxide content to 23% (molar content) have been made and their properties studied. Microspheres with diameter 20 – 32 μm for use in brachytherapy have been made. These microspheres are characterized by a completely amorphous structure with high shape isometry (particle asphericity < 5%), high chemical stability, and no crystalline inclusions.

Key words: yttrium aluminosilicate glasses, glass microspheres, nuclear medicine.

Yttrium aluminosilicate glasses have a wide spectrum of applications in modern industry: as optical amplifiers and lasers [1], media for binding radioactive wastes [2], high-temperature coatings on composite materials, and additions facilitating sintering of carbide and nitride ceramics [3, 4]. These glasses are radiation resistant, nontoxic, and chemically stable, which eliminates the problem of radioactive materials leaching out of the glass matrix [5, 6].

Microspheres made of aluminosilicate-based glass with a nearly monodisperse diameter distribution are used in radiotherapy as a radiation delivery medium for treating tumors in different organs in humans, particularly, the liver. This therapy is especially important for cancers with an unfavorable prognosis. In this connection, there is great interest in Y_2O_3–Al_2O_3–SiO_2 (YAS) glasses and microspheres based on them [7 – 10]. However, in Russia YAS spheres for treating cancer started to be used only in the course of the present work.

Before microspheres are introduced into the human body they are irradiated with thermal neutrons in a nuclear reactor. As a result, the short-lived isotope ^{90}Y with half-life 64.1 h sufficient for delivering a preparation to a clinic and performing treatment is formed in the YAS glass. The ^{90}Y isotope possesses nuclear-physical characteristics which are convenient for therapeutic applications: β-radiation energy 2.28 MeV, maximum travel distance in soft tissue 12 mm, and average radiation penetration range 2.8 mm. The aluminum and silicon oxides present in the glass base do not form long-lived isotopes when irradiated and impart high chemical stability to the preparation in the internal medium of the body (blood plasma pH ≈ 7.4).

I. A. Bondar' and F. Ya. Galakhov were the first to study the system Y_2O_3–Al_2O_3–SiO_2 by the quenching method [11]. They constructed the phase diagram and described the liquidus surface and the phase ratios. They observed glass formation on the SiO_2-enriched section. The ternary eutectic temperature was 1345°C. The glass-formation region in the Y_2O_3–Al_2O_3–SiO_2 system was studied in [12]. The authors of this work synthesized glass in platinum foil with a 2 g batch at temperature 1650 – 1700°C with the crucible allowed to cool in air. They also showed that yttrium aluminosilicate glass is stable in alkali solutions and possess a high elastic modulus and refractive index [12]. A nonequilibrium diagram is also known; this diagram was obtained by rapid melting induced by a CO_2 laser with auto-quenching [13]. The data obtained for YAS glasses and the properties of these glasses are also presented in [14, 15]. It must be underscored that in [11 – 15] glasses with no admixtures of a crystalline phase were obtained in the temperature range 1500 – 1700°C using 2 – 50 g charges with more than 25% Y_2O_3. In addition, glasses without crystallization were obtained with content 25%[3] Y_2O_3 (melting temperature 1700°C, 2 g charge) and 21% Y_2O_3 (melting temperature 1600°C, 50 g charge). The presence of impurities in the crystalline phase is ex-

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[3] Here and below, the molar content unless stipulated otherwise.

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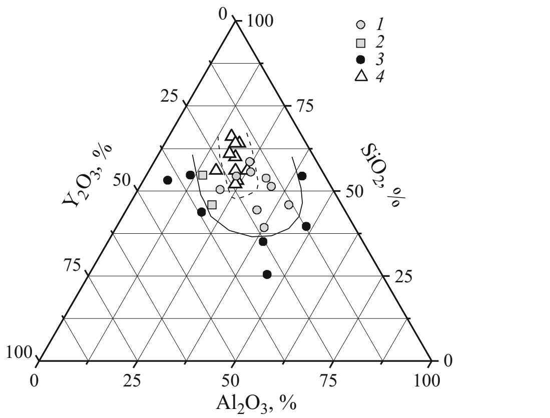

Fig. 1. Region of glass formation in the system Y_2O_3–Al_2O_3–SiO_2 (molar content): *1*) glass; *2*) partial crystallization; *3*) crystallization (*1 – 3* according to the data of [17]); *4*) glass obtained in the present work in a 300 ml crucible; dashed line) glass-formation region.

tremely undesirable for microspheres to be used as a delivery medium, because the microspheres can crack even during irradiation in a reactor and radioactive yttrium can enter the patient's body. For this reason, the results of [11 – 15] must be clarified considerably, especially when the objective is to obtain crystallization-free glass in large volumes for medical applications.

In [16] YAS glass with 27 – 35.6% Y_2O_3 was obtained by high-temperature synthesis at elevated pressure and centrifuging. This method is hardly promising for use in nuclear medicine because of a large amount of impurity metals, forming long-lived radioactive isotopes, can enter the glass.

The sol-gel method can be used to obtain YAS glass [17]. Drawbacks of this method are the high cost of precursors (mainly, alkoxides), the complexity of the production technology, the long duration of the process (weeks) with high energy consumption, and a low yield of the finished product.

TABLE 1. Compositions, Glass Density ρ, Glassmaking temperature t_g , and yttrium ion concentration N_Y of the Synthesized Glasses

Glass composition	Molar content, %			ρ, g/cm^3	t_g, °C	N_Y, ions/cm^3
	Y_2O_3	Al_2O_3	SiO_2			
1	17	19	64	3.29	885	6.99896×10^{21}
2	18	16	66	3.35	886	7.5145×10^{21}
3	18	18	64	3.38	882	7.51663×10^{21}
4	19	25	56	3.42	884	7.66711×10^{21}
5	20	20	60	3.39	900	8.03422×10^{21}
6	21	18	61	3.48	889	8.59059×10^{21}
7	22	22	56	3.55	887	8.89141×10^{21}
8	23	24	53	3.60	894	9.20924×10^{21}
9	24	24	52	3.66	892	9.62249×10^{21}
10	27	17	56	3.69	904	1.07151×10^{22}

In [18, 19] microspheres were obtained from glass with composition (molar content of oxides) 17 Y_2O_3, 19 Al_2O_3, and 64 SiO_2, melted at temperatures 1500 – 1600°C in a platinum or corundum crucible for 2 – 5 h in an electric furnace with complete homogenization of the melt and extraction of the melt into water or onto a steel plate followed by quenching. The glass was ground into powder, which was formed into microspheres in the oxygen flame of a burner. This YAS-glass composition has found application in nuclear medicine for treating metastasis in the liver. The effectiveness of the treatment with microspheres increases as the amount of yttrium atoms in the preparation increases, but the amount of preparation introduced into a patient's body must be as low as possible. For this reason, it is very desirable to increase the Y_2O_3 content in the microspheres and, correspondingly, increase the effectiveness of the finished preparation at lower cost. Increasing the yttrium oxide content in the microspheres gives the possibility, as yet unrealized, of creating on the surface of the spheres an yttrium-depleted layer that prevents yttrium from entering the body while maintaining the irradiation dose.

The present work is concerned with the problem of synthesizing YAS glass with elevated yttrium oxide content in volumes smaller than 200 ml and producing 20 – 32 μm microspheres from these glasses. For this, we investigated the range of compositions with 17 – 27% Y_2O_3 and the following ratios of the components in the glass (%): 17 – 27 Y_2O_3, 16 – 25 Al_2O_3, and 52 – 66 SiO_2. The glass compositions were chosen in the eutectic region of the ternary system (Fig. 1).

The ultrapure-grade reagents Y_2O_3, amorphous SiO_2, and $Al(OH)_3$ were used as the raw materials. The batch components prepared beforehand were mixed for 2 h in a KV-1 quartz-glass container. YAS glass was made in a 250 cm^3 dispersion-hardened platinum crucible at temperatures 1600 – 1650°C in a specially constructed electric furnace with SiC heaters; the working chamber of the furnace was made of high-purity corundum. The soaking time at the maximum temperature corresponding to complete homogenization of the glass mass did not exceed 2 h. The synthesized compositions are presented in Table 1.

The glass was produced by quenching melt poured onto a metal plate and rolled with cylindrical metal rollers as well as by rolling melt through water-cooled metal rollers made of high-temperature steel and rotating at 1500 rpm. These production methods guarantee that there will be no crystalline inclusions and made it possible to obtain amorphous plates of different thicknesses up to 100 μm.

A LDI-65 laboratory grinder with corundum wheels was used for grinding, and a Retsch AS 200 analytical sieve shaker with a wet sieving function was used for classifying the glass powder. The powders obtained with dispersity in different ranges (15 – 35, 20 – 32, 20 – 50 μm, and others) were used to obtain microspheres by melting glass powder in plasma flow in a 25-kW electrocorundum plasmatron.

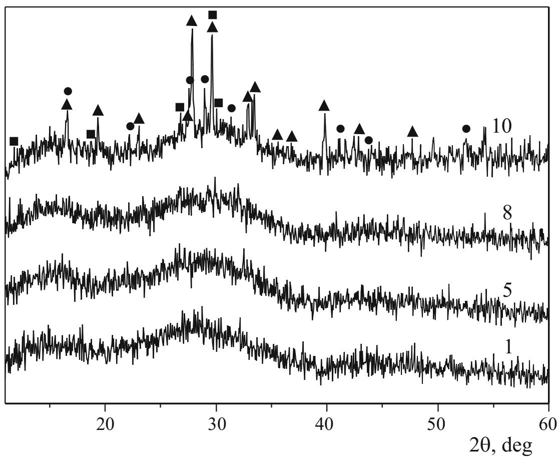

Fig. 2. X-ray diffraction patterns of glass powders with the compositions: 1) $17Y_2O_3 - 19Al_2O_3 - 64SiO_2$; 5) $20Y_2O_3 - 20Al_2O_3 - 60SiO_2$; 8) $23Y_2O_3 - 24Al_2O_3 - 53SiO_2$; 10) $27Y_2O_3 - 17Al_2O_3 - 56SiO_2$; ▲) $Y_2Si_2O_7$; ●) γ-$Y_2Si_2O_7$; ■) $Al_2Y_4O_9$.

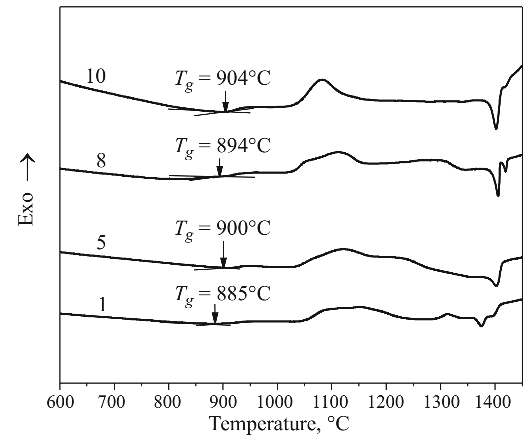

Fig. 3. DTA curves for glass powders with the compositions: 1) $17Y_2O_3 - 19Al_2O_3 - 64SiO_2$; 5) $20Y_2O_3 - 20Al_2O_3 - 60SiO_2$; 8) $23Y_2O_3 - 24Al_2O_3 - 53SiO_2$; 10) $27Y_2O_3 - 17Al_2O_3 - 56SiO_2$. The numbers on the curves correspond to the numbers of the glass samples (see Table 1).

The glass samples obtained were comminuted in an agate mortar and analyzed by means of x-ray phase analysis (XPA). A DRON-3M diffractometer (CuK_α radiation, nickel filter) was used to record the x-ray diffraction patterns of the glasses.

A Netsch STA 449 thermal analyzer was used to perform differential thermal analysis (DTA) in a regime with temperature rising uniformly at the rate 10 K/min to 1450°C. The glass density was measured by hydrostatic weighing in water using a YDK 01 density determination kit for the Sartorius GC 803S-OCE scales.

A JEOL JSM-6380 LA microscope with a JET 2300 x-ray microanalyzer was for scanning electron microscopy. The accelerating voltage was 25 kV. To prevent charging of the microspheres a layer of gold was deposited on their surface beforehand.

Glass with no indications of crystallization was obtained for compositions with up to 23% Y_2O_3. The x-ray diffraction patterns of glass powder with ≤ 23% Y_2O_3 showed that the glasses synthesized were completely amorphous. For > 23% Y_2O_3 in YAS glasses, glass with no indications of crystallization cannot be obtained by the quenching methods used (Fig. 2). Crystallization was already observed during the formation process in glass with 27% Y_2O_3. Three crystalline phases, identified as $Y_2Si_2O_7$, γ-$Y_2Si_2O_7$, and $Al_2Y_4O_9$, were found in this sample.

The DTA curves of powdered YAS-glass samples for the compositions 1, 5, 8, and 10 are presented in Fig. 3. The presence of wide exothermal peaks indicates that crystallization processes are weak. Glass with the composition $27Y_2O_3 - 17Al_2O_3 - 56SiO_2$ is characterized by the most intense crystallization.

As shown in Fig. 4, the density of the glasses obtained varies from 3.29 to 3.66 g/cm^3 depending on the yttrium

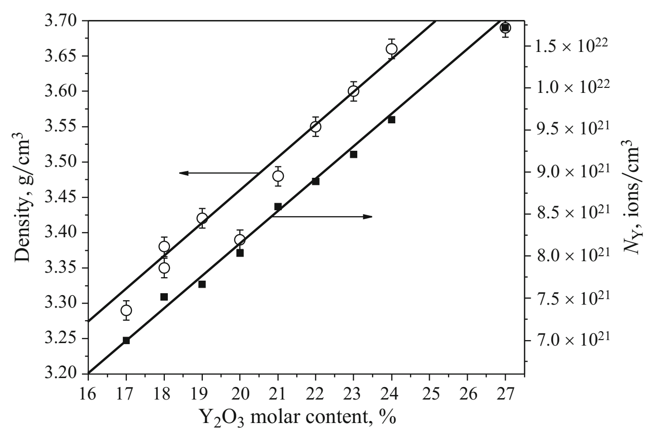

Fig. 4. Plots of the density and number of yttrium ions per cm^3 versus the Y_2O_3 content in YAS glasses: ○) density; ■) number of ions.

oxide content. The density increases as a function of not only the increase in the Y_2O_3 amount but also the ratio Al_2O_3/SiO_2. The concentration of yttrium ions varies from 7.00×10^{21} to 1.07×10^{22} ions/cm^3. The density data for the experimental glasses and the volume content of the yttrium ions are presented in Table 1.

The chemical stability of plate-shaped YAS-glass samples with Y_2O_3 content to 17% as determined from the mass change of a sample after soaking in distilled water and in HCl (pH = 2) at temperature 37°C for four weeks (the time period over which the residual radioactivity of Y^{90} becomes negligibly small) was less than 0.1 and 2.7 mg/cm^2, respectively.

As one can see from Fig. 5, obtained by the SEM method, the YAS-microsphere particles have a regular spherical shape. The surface of the microspheres is uniform; there

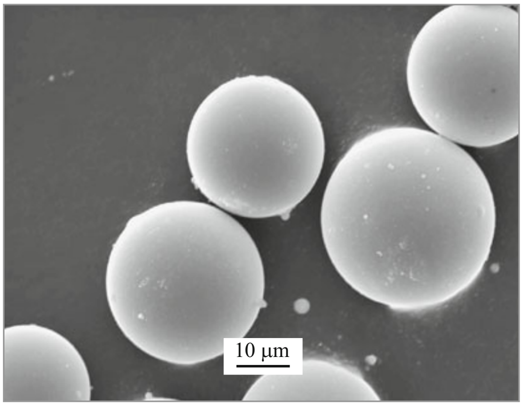

Fig. 5. SEM image of YAS microspheres.

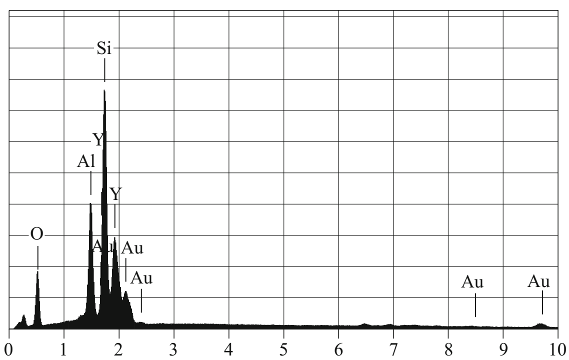

Fig. 6. XSPA spectra of YAS microspheres; gold presence is due to gold deposition on the sample.

TABLE 2. Glass with the Composition (Molar Content, %) $17Y_2O_3 - 19Al_2O_3 - 64SiO_2$

Element	Average elemental content, %		Compound	Content, wt.%
	By weight	Molar		
O	35			
Al	8	16	Al_2O_3	15
Si	16	63	SiO_2	35
Y	30	18	Y_2O_3	38
Au	11	3	Au_2O_3	12

are no pores or microcracks. The glass composition was determined by x-ray spectral microanalysis (XSMA). A typical spectrum and the results of the elemental determination are presented in Fig. 6 and Table 2 for glass with the composition 1.

XSMA was used to study the distribution of the principal elements on the surface of the microspheres. The elemental maps so obtained are displayed in Fig. 7. Evidently, the spatial distribution of the principal elements — Al, Si, and Y — on the surface of a sphere is the same, indicating that its composition is uniform.

The grinding regimes were chosen so as to minimize the amount of grinding required. It was determined that grinding to a prescribed specific surface area of YAS-glass produced in the form of chips required approximately one-third the time required to grind the granular material obtained by comminuting a monolithic glass founding. As a result of this, grinding glass consisting of chips is much less energy-intensive (by a factor of 2 – 3) and, in addition, more efficient than grinding a founding, since the amount of milling and dust fraction with particles smaller than about 5 μm is sharply lower (more than two-fold) than in the glass powder obtained (Fig. 8).

It was established experimentally that grinding glass chips no more than 200 μm thick is closest to being optimal for obtaining 20 – 32 μm microspheres (the most widely used sizes in brachytherapy). Plasmatron spheroidization of powders made it possible to obtain microspheres suitable for brachytherapy. The microspheres were characterized by a fire-polished surface (Fig. 9) and their diameters were 20 – 32 μm (the < 15 μm fraction comprised about 4%, and no > 32 μm particles were present). They exhibited a completely amorphous structure with no crystalline inclusions, high shape isometry (particle asphericity < 5%), and high chemical stability (first hydrolytic class).

In summary, it was established experimentally that YAS glasses with up to 23% Y_2O_3 and no crystalline phase can be obtained in volumes of the order of 300 ml at high melting temperatures (to 1650°C) and using the method of intense cooling of the melt. Microspheres containing 23% Y_2O_3 exhibited completely amorphous structure with high shape

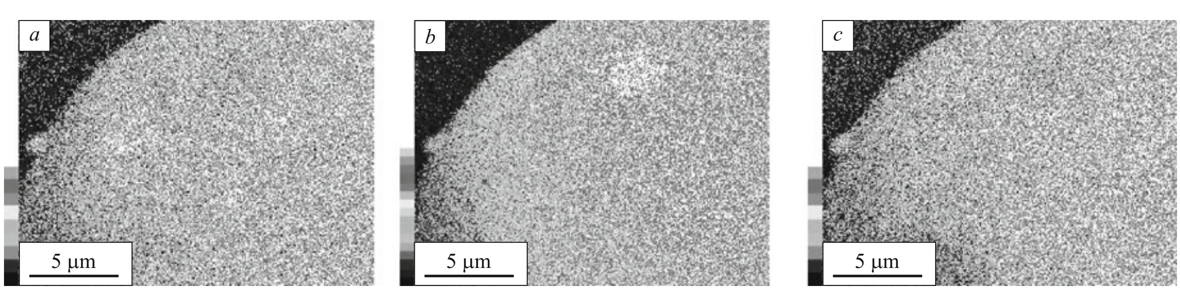

Fig. 7. XSMA elemental maps of Al (*a*), Si (*b*), and Y (*c*).

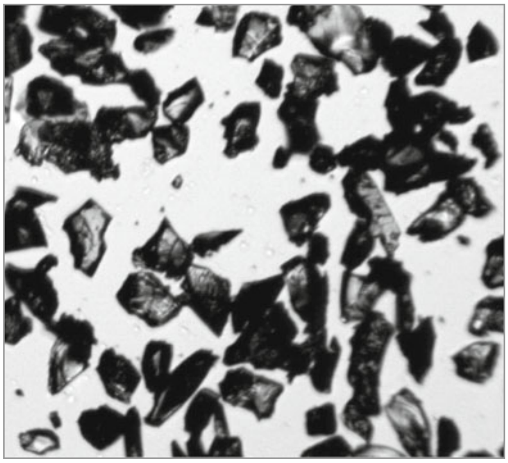

Fig. 8. Photomicrograph of YAS-glass powder obtained by grinding in a glass-chip grinder; ×400.

Fig. 9. Reflected light photomicrograph of 20 – 32 μm in diameter YAS-glass microspheres; ×440.

isometry, high chemical stability (first hydrolytic class), and no crystalline inclusions.

The first surgical operations using yttrium aluminosilicate microspheres in people were successfully performed in the Russian Federation in May 2011 at State Clinical Hospital No. 55.

This work was performed with the financial support of the Ministry of Education and Science of the Russian Federation (grant 11.G34.31.0027). We thank the IBt Bebig Company for performing the studies of the microstructure and the analysis of the chemical composition of the microspheres.

REFERENCES

1. P. Jander and W. S. Brocklesby, “Spectroscopy of yttria – alumina – silica glass doped with thulium and erbium,” *IEEE J. Quantum Electron.*, **40**, 509 (2004).
2. L. Bois, N. Barre, S. Guillope, et al., “Aqueous alteration of lanthanum alumino-silicate glasses,” *J. Non-Cryst. Solids*, **276**, 181 – 194 (2000).
3. J. Marchi, D. S. Morais, J. Schneider, et al., “Characterization of rare earth aluminosilicate glasses,” *J. Non-Cryst. Solids*, **351**, 863 – 868 (2005).
4. P. Lichvar, P. Sajgalik, J. Liska, and D. Galusek, “CaO–SiO_2–Al_2O_3–Y_2O_3 glasses as model grain boundary phases for Si_3N_4 ceramics,” *J. Eur. Ceram. Soc.*, **27**, 429 (2007).
5. S. Iftekhar, J. Grins, P. N. Gunawidjaja, and M. Eden, Glass formation and structure-property-composition relations of the RE_2O_3–Al_2O_3–SiO_2 (RE = La, Y, Lu, Sc) systems,” *J. Am. Ceram. Soc.*, **94**, 2429 – 2435 (2011).
6. J. Du, “Molecular dynamics simulations of the structure and properties of low silica yttrium aluminosilicate glasses,” *J. Am. Ceram. Soc.*, **92**, 87 – 95 (2009).
7. E. M. Erbe and D. E. Day, “Chemical durability of YO_3–Al_2O_3–SiO_2 glasses for the in vivo delivery of beta radiation,” *J. Biomed. Mater. Res.*, **27**, 1301 – 1308 (1993).
8. B. I. Carr, “Hepatic arterial ^{90}yttrium glass microspheres (therasphere) for unresectable hepatocellular carcinoma: interim safety and survival data on 65 patients,” *Liver Transpl.*, **10**, Suppl. 1, 107 – 110 (2004).
9. R. Salem and K. G. Thurston, “Radioembolization with yttrium-90 microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Pt. 3: Comprehensive literature review and future direction,” *J. Vasc. Interv. Radiolol.*, **17**, 1571 – 1594 (2006).
10. L. L. Hench, D. E. Day, Wolfram Holand, and Volker M. Rheinberger, “Glass and medicine,” *Int. J. Appl. Glass Sci.*, **1**, 104 – 117 (2010).
11. I. A. Bondar’ and F. Ya. Galakhov, “Phase equilibria in the system Y_2O_3–Al_2O_3–SiO_2,” *Izv. Akad. Nauk SSSR, Ser. Khimich.*, No. 7, 1325 – 1326 (1964).
12. O. V. Mazurin, M. V. Strel’tsina, and T. P. Shvaiko-Shvaikovskaya, *Properties of Glasses and Glass-Forming Alloys. Vol. 3. Ternary Silicate Oxide Systems,* Izd. Akad. Nauk SSSR, Leningrad (1970).
13. R. Harryson and P. Vomacka, “Glass formation in the system Y_2O_3–Al_2O_3–SiO_2 under conditions of laser melting,” *J. Eur. Ceram. Soc.*, **14**, 377 – 381 (1994.).
14. M. J. Hyatt and D. E. Day, “Glass properties in the yttria-alumina-silica system,” *J. Am. Ceram. Soc.*, **70**, 283 – 287 (1987).
15. J. E. Shelby, S. M. Minton, C. E. Lord, and M. R. Tuzzolo, “Formation and properties of yttrium aluminosilicate glasses,” *Phys. Chem. Glasses,* **33**, 93 – 98 (1992).
16. B. He, G. Liu, J. Li, et al., “Preparation of Y_2O_3–Al_2O_3–SiO_2 glasses by combustion synthesis melt–casting under high gravity,” *Mater. Res. Bull.*, **46**, 1035 – 1038 (2011).
17. James C. Walck and Carlo G. Pantano, “Sol-gel processing and crystallization of yttrium aluminosilicates,” *J. Non-Cryst. Solids*, **124**, 145 – 154 (1992).
18. G. J. Ehrhardt and D. E. Day, “Therapeutic use of Y-90 microspheres,” *Nucl. Med. Biol.*, **14**, 233 – 242 (1987).
19. D. E. Day and G. J. Ehrhardt, *Microspheres for Radiation Therapy, U.S. Patent 5,302,369*.